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Original Article

CORRELATION BETWEEN SERUM ADIPOKINES WITH LIVER CELL DAMAGE IN NON-OBESE CHRONIC HEPATITIS C EGYPTIAN PATIENTS

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ABSTRACT

Background: Hepatitis C virus (HCV) continues to be a major disease burden on the world, especially in Egypt, which may progress to cirrhosis. Adipokines are implicated in regulation of the inflammatory response, angiogenesis and fibrogenesis. Some adipokines have a protective effect while others have negative effect in chronic hepatitis C (CHC).

Aim of the study: We aimed to study the new adipokines (visfatin, chemerin and omnetin1) in CHC patients to find out its relation to the biochemical liver functions tests and liver histopathology in non-obese chronic hepatitis C patients

Patients and methods: This study included 70 patients with CHC and 20 healthy individuals as a control group. Liver function tests, serum visfatin, chemerin and omentin1 levels were measured. Percutaneous liver biopsy was performed in CHC patients.

Results: The three adipokines levels were significantly increased in CHC patients comparing to control group (P<0.001). Serum visfatin and chemerin levels were negatively correlated with necro-inflammatory activity grade and fibrosis stage (P= 0.032,0.043, 0.029,0.036) respectively and not correlated with HOMA-IR (P= 0.236, 0.225), while serum omentin1 was not correlated with necro-inflammatory activity grade and fibrosis stage (P=0.230,0.312)but negatively correlated with HOMA-IR (P=0.031).

Conclusion: The three adipokines levels were significantly elevated in CHC patients indicating their possible involvement in the pathogenesis of the disease and its metabolic complications. Serum visfatin and chemerin concentration may serve as an additional tool in determining more advanced grades of necro-inflammatory activity grade and fibrosis stage. While serum omentin-1 can predict the severity of insulin resistance.

KEYWORDS: Chronic Hepatitis C, Adipokines, Visfatin, Chemerin and Omnetin1, Liver, HOMA-IR

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INTRODUCTION

Chronic hepatitis C (CHC) has features of a viral disease and a metabolic liver disease that includes insulin resistance (IR), liver steatosis, disturbed lipid and glucose metabolism (1).

Hepatitis C virus (HCV) can provoke IR by direct action and by stimulation of inflammatory processes and/or fibrosis. Number of studies suggest that IR is markedly related to the extent of steatosis, inflammatory activity in the liver and the progression of fibrosis (2,3). IR also emerges to increase the risk of developing liver cancer.Adipose tissue (AT) is considered as an energy storage and as an active endocrine organ. AT synthesizes and secretes a diversity of bioactive peptides, formerly recognized as “adipokines (4).

Adipokines are implicated in regulation of the inflammatory response, angiogenesis and fibrogenesis (5-6).

Therefore, adipokines in cooperation with IR appear to participate in the pathogenesis and progression of liver disease. It has been proposed that some adipokines have a protective effect while others have negative effect in CHC (5-7).

Visfatin is an adipokine produced by a diversity of cells as lymphocytes, monocytes, neutrophils, hepatocytes, adipocytes and pneumocytes. Visfatin levels are increased in both acute and chronic inflammatory diseases (8-9).

Visfatin has many immunomodulating and proinflammatory properties.

It can act as a cytokine that stimulates B-cell maturation and prevent neutrophil apoptosis (10-11).Visfatin improves activation of leukocytes, synthesis of adhesion molecules, production of proinflammatory cytokines(8-9) and simulation of proangiogenic activity (12).

Another member of the growing adipokine family is chemerin. It is highly expressed in various tissues including ;white adipose tissue, liver and lungs (13). It has both proinflammatory effect by stimulating and enrolling natural killers cells and macrophages into inflamed tissue(14-16), and an anti-inflammatory effect by preventing synthesis of proinflammatory mediators and activating adiponectin expression (14,16,17).

Omentin is an adipokine specially released by visceral AT (18). Omentin increases insulin-stimulated glucose uptake in human adipocytes via Akt signaling and its expression in visceral AT is reduced in obesity and insulin resistance (18-19). Omentin decreased *in vitro* migration and angiogenesis in human endothelial cells (20). Herder et al. (21) suggested that omentin acts via upregulation of adiponectin, which in turn affects lipid metabolism and indirectly decrease insulin resistance. In this study we aimed to throw light on the new adipokines (visfatin, chemerin and omentin1) in CHC patients to find out its relation to the biochemical liver functions tests and liver histology in non-obese chronic hepatitis C patients

Subjects and Methods

The study was approved by the Ethics Committee of the Faculty of Medicine, Tanta University **);** and conducted in accordance with the Helsinki Declaration. Written informed consent was obtained from each subject prior to any study procedure, with assurance of patient privacy. The study was performed in the internal medicine department of Tanta university hospitals. The study included 90 individuals who were divided into two groups:

Group1: 70 patients with chronic hepatitis C with average age (49.3 ± 4.2years) with persistently elevated alanine aminotransferase (ALT) for at least 6 months. CHC diagnosis was based on the presenc e of anti-HCV antibodies and HCV RNA in serum for at least 6 months. They were 52males and 18 females. The mean of their body mass index was 21.0±2.3 kg/m^2.

Group2: 20 healthy individuals of matched age & sex as controls. Their average age was (43.2 ± 4.2 years). They were 14 males and 6 females with mean of their body mass index was 19.7±2.1 kg/m^2. Patients with history of the following disorders were excluded from the study: Hepatitis B virus and auto immune hepatitis, Patients receiving hepatotoxic drugs or alcohol intake and conditions associated with high adipokines values also were excluded such as:diabetes mellitus, obesity persons whose body mass index $\geq$ 30 kg/m^2, renal failure, heart failure, known malignant disease, systemic inflammatory disease or autoimmune disease.

Data Collection

All patients were subjected to the following; full history taking, thorough general and abdominal clinical examination, laboratory investigations(fasting blood sugar level, complete blood count, liver biochemical profile, prothrombin time and activity, lipid profile, renal function tests, alpha fetoprotein. The hepatitis seromarkers HBsAg for HBV and anti-HCV were tested using ELISA (Abbott laboratories). The amount of HCV RNA in serum samples was quantified using a realtime PCR Step One instrument and software (Applied Biosystems). The degree of IR was calculated according to the homeostasis model assessment for IR (HOMA-IR) by the formula: fasting insulin level (mUI/L) x fasting glucose level (mg/dL)/405(22).

Markers Assay

Blood samples were obtained the morning after a 12-hour overnight fast. Samples were immediately centrifuged at 1000 g for 15 minutes. Serum samples were stored at -20°C for subsequent assay using an enzyme-linked immuno sorbent assay according to the manufacturer's instructions. Serum insulin by Quantikine® ELISACatalog Number DINS00 Intra-Assay: CV<4%, Inter-Assay: CV<7.5%. Serum visfatin, chemerin and omentin 1 were assayed by (RayBio® Human/ Mouse/ Rat Visfatin Enzyme Immunoassay Kit Catalog #: EIA-VIS, EIAM-VIS, EIAR-VIS, intra-assay: CV<10%, inter-assay: CV<15% ; Quantikine® ELISA Human Chemerin Immunoassay Catalog Number DCHM00,intra-assay: CV 2.8-4.5%, inter-assay: CV 6.4-7.9 % ; Aviscera Bioscience Catalog No SK00020-01,intra-assay: CV4-6%, inter-assay: CV8-10% respectively). A conventional abdominal ultrasonography and guided liver biopsy required for histopathological examination to assess the grade of inflammation and stage of fibrosis according to the Metavir scoring system (23) and to exclude any combined liver insults. Serum samples were withdrawn at time of biopsy. Metavir scoring system demonstrated different stages of fibrosis (F0-F4) and grades of necro-inflammatory changes (A0-A3). The histopathological examination of all the liver biopsies was performed by a single hepatology expert pathologist.

Statistics

Statistical presentation and analysis of data in the present study was carried out; continuous data were expressed as mean ± SD, whereas categorical data were expressed as number and percentage. Categorical data were compared using the X^2 test. Continuous data between two groups were compared using Student's t-test. Pearson and Spearman correlations between different parameter were used. Statistical significance was defined as a P-value of less than 0.05. Analyses were carried out using the SPSS program, version 17 (SPSS Inc., Chicago, Illinois, USA) and the GraphPad Prism software (Graph-Pad Prism Software Inc., San Diego,California, USA).

RESULTS

The laboratory data of studied groups and histopathological features of the CHC patients group were illustrated in Table 1.

Table 1: The Laboratory Data of Studied Groups and Histopathological Features of the CHC Patients Group

Variables	Chronic Hepatitis C (N=70) Group I Mean ± SD	Control Group (N=20) Group II Mean ± SD	*P* Value
Platelets ($x10^3/cm^3$)	236.3 ±147.5	251.1±192.1	0.140
INR	1.2± 0.09	0.99± 0.11	0.947

Table 1: Contd.,			
Total bilirubin (mg/dL)	0.78± 0.14	0.68± 0.15	0.906
Serum ALT(U/L)	67.6± 14.09	29.9± 3.98	<0.001*
Serum AST (U/L)	54.1±10.9	30.8± 4.46.2	<0.001*
Albumin (gm/dL)	4.2± 0.26	4.9± 0.2	0.176
HDL(mg/dL)	55.3±1.6	54.9±1.5	0.30
LDL(mg/dL)	70.2±4.1	69.6±3.1	0.54
Fasting blood glucose (mg/dL)	95.1±11.4	93.3±9.4	0.934
HOMA-IR	2.3±0.15	1.67±0.12	0.015*
Serum visfatin (ng/ml)	62.9±55.3	21.2±2.5	<0.001*
Serum chemerin (ng/ml)	3.6±0.48	2.3±0.37	<0.001*
Serum omentin-1 (ng/ml)	20.1±2.5	11.7±0.58	<0.001*
Grade of inflammation **A1** **A2** **A3**	 24(34.3%) 27(38.6%) 19(27.1%)		
Stage of fibrosis **F1** **F2** **F3**	 18(25.7%) 28(40%) 24(34.3%)		

ALT; alanine aminotransferase enzyme, AST; aspartate aminotransferase enzyme, HDL; high density lipoprotein, LDL; low density lipoprotein. Values of P < 0.05 are considered statistically significant

HOMA-IR significantly increased in patients with CHC (2.3±0.15 vs1.67±0.12, *P* = 0.015).Serum visfatin levels were significantly higher in CHC patients group compared to control group (62.9±55.3 vs 21.2±2.5 ng/mL, *P*<0.001), serum chemerin levels also significantly increased in patients with CHC (3.6±0.48 vs 2.3±0.37 ng/mL, *P*<0.001). Serum omentin1 concentration was significantly increased in CHC patients compared to control group(20.1±2.5 vs 11.7±0.58 ng/mL, *P*<0.001). (Table 1)

Histopathological Examination of Liver Tissue Samples

The histopathologic results of liver biopsy in group 1 patients according to Metavir classification revealed necro-inflammatory activity grade 1 in 24 patients, grade 2 in 27 patients, and grade 3 in 19 patients. The results showed fibrosis stage 1 in 18 patients, stage 2 in 28 patients, and stage 3 in 24 patients. (Table 1)

According to HCV RNA level in group 1; 29 patients (41.4%) with low viraemia (up to 10^5 copies/ml), 31 patients (44.3%) with moderate viraemia (10^5-10^6 copies/ml), while 10 patients (14.3%) with high viraemia more than 10^6 copies/ml.

Table 2: Correlation between Serum Visfatin, Serum Chemerin and Serum Omentin-1 with Different Parameters in Chc Patients Group

Variable	Serum Visfatin (ng/ml)		Serum Chemerin (ng/ml)		Serum Omentin-1 (ng/ml)	
	Coeff.	*P*	Coeff.	*P*	Coeff.	*P*
Age (years)	0.102	0.335	0.182	0.132	0.093	0.442
BMI kg/m^2	0.394	0.031*	0.135	0.132	0.105	0.389
Viral Load copies/ml	0.19	0.34	0.45	0.26	0.28	0.52
ALT(U/L)	0.27	0.21	-0.242	0.043*	0.272	0.026*

Table 2: Contd.,						
AST(U/L)	0.254	0.215	-0.258	0.031*	0.227	0.039*
Total bilirubin(mg/dL)	0.27	0.31	-0.251	0.036*	-0.121	0.320
Albumin(gm/dL)	-0.153	0.415	-0.166	0.170	0.084	0.490
INR	-0.174	0.35	-0.268	0.042*	0.068	0.142
HOMA-IR	-0.156	0.09	-0.147	0.225	-0.258	0.031*
Activity grade	-0.601	0.001*	-0.109	0.029*	0.037	0.230
Fibrosis stage	-0.45	0.012*	-0.251	0.036*	0.068	0.312

Relation of Serum Visfatin, Chemerin and Omentin 1 with Some Analyzed Variables in CHC Group

There was significant positive correlation between the serum visfatin level and BMI (r =0.394; *P*= 0.031). While there were significant negative correlations between the serum chemerin levels with ALT (r =-0.242; *P*= 0.043), AST (r =-0.258; *P*= 0.031), total bilirubin (r =-0.251; *P*= 0.036) and INR(r =- 0.268; *P*= 0.042). Serum omentin 1 levels were positively significantly correlated with ALT (r =0.272; *P*= 0.026) and AST (r =0.227; *P*= 0.039). Serum omentin 1 levels were negatively correlated with HOMA-IR (r=-0.258, *P*= 0.031), while serum visfatin and chemerin levels showed no significant correlation with HOMA-IR *(P* =0.09, 0.225) respectively. (Table 2&Figure3)

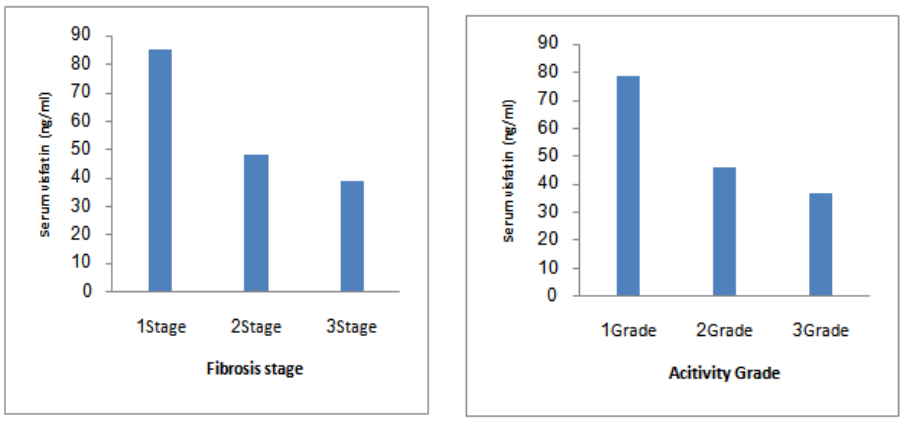
Table 3: Comparison between Adipokine Levels Regarding Liver Histopathology Results in CHC Patients Group

Liver Biopsy		Serum Visfatin (Ng/Ml)	*P Value* Table 3. Comparison Between Adipokine Levels Regarding Liver Histopathology Results in Chc Patients Group	Serum Chemerin (Ng/Ml)	*P Value*	Serum Omentin-1 (Ng/Ml)	*P Value*
Activity grade	Grade 1 (N=24)	78.7±60.1	0.000*	3.5±0.5	0.000*	17.9±2.5	0.087
	Grade 2 (N=27)	45.90±14.3		3.2±0.9		18.4±3.1	
	Grade 3 (N=19)	37.05.±17.0		2.1±0.6		19.7±2.1	
Fibrosis stage	Stage 1 (N=18)	84.83±77.82	0.046*	3.9±1.0	0.000*	19.4±1.9	0.284
	Stage 2 (N=28)	47.83±17.16		3.7±0.8		20.1±2.8	
	Stage 3 (N=24)	38.78.±17.35		2.3±0.9		18.9±3.1	

Relation of Serum Visfatin, Chemerin and Omentin 1 with Liver Histopathology in CHC Group

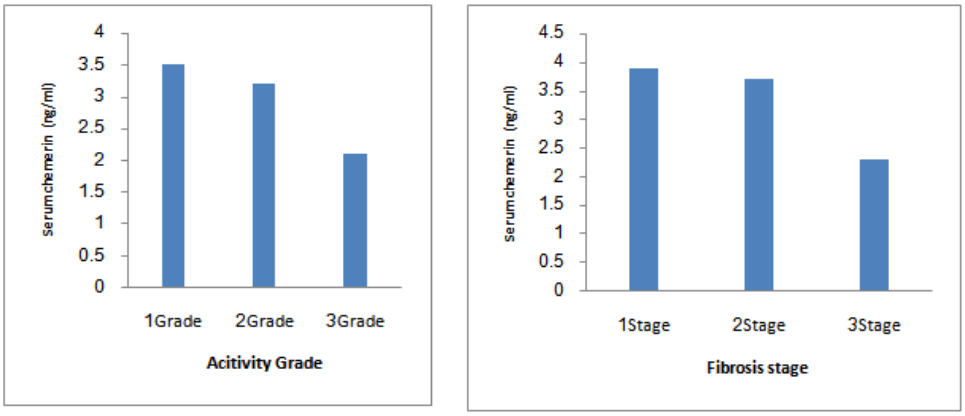
Serum visfatin levels were negatively correlated with the grade of necro-inflammatory activity as shown in Table 2 & 3 (r = -0.601, ***P***= 0.001). The lowest levels were detected in patients with the most advanced inflammation; grade 1: 78.73±60.1(ng/ml), grade 2: 45.90±14.63 (ng/ml) and grade 3 : 37.05±17(ng/ml) (Figure1A). Regarding the fibrosis stages, there was significant negative correlation between serum visfatin level and the fibrosis stages (r = -0.45, ***P*** = 0.012). There was decreasing levels with advanced staging as shown; stage 1: 84.83±77.82, stage 2: 47.83±17.16 and stage 3: 38.78.±17.35) (Figure1B).Serum chemerin levels were also negatively correlated with the grade of necro-inflammatory activity as shown in Table 2&3 (r = -0.109, *P*= 0.029). The lowest levels of chemerin were found in patients

with increased inflammation as grade 3: 2.1±0.6, grade 2 : 3.2±0.9, grade 1: 3.5±0.5ng/mL, *P* = 0.000) (Figure 2A). Concerning the fibrosis stages, there was also a significant negative correlation between serum chemerin levels and the fibrosis stages (r = -0.251, *P* = 0.036). Moreover, the chemerin levels decreased with increasing stages of fibrosis; stage 1: 3.9±1.0, stage 2: 3.7±0.8and stage 3: 2.3±0.9ng/mL (Figure 2B). There was no significant difference in serum omentin1 levels with either necro-inflammatory activity grade or stages of fibrosis *(P* =0.230, 0.312) respectively. (Table 2&3)



(A) **(B)**

Figure 1: Serum Visfatin in Different Necro-Inflammatory Activity Grade (A) and Fibrosis Stage (B) in CHC Patients



(A) **(B)**

Figure 2: Serum Chemerin in Different Necro-Inflammatory Activity Grade (A) and Fibrosis Stage (B) in CHC Patients

DISCUSSIONS

Insulin resistance (IR) is a characteristic of metabolic disturbances occurred in chronic hepatitis C patients. Intensification of IR enhances fibrosis progression and inflammatory activity (1-2).

The current study revealed that serum visfatin levels were significantly elevated in chronic hepatitis C patients compared to the controls, which suggest that visfatin may play an important role in the regulation of the inflammatory process in CHC. Visfatin enhances the production of IL-1β, TNF-α, and especially of IL-6. Some studies revealed that visfatin is upregulated by IL-6(24).

Visfatin stimulate TNFα production in human peripheral blood mononuclear cell. Increased serum TNFα level was observed in CHC and it was positively associated with necro-inflammatory grade. TNFα starts apoptosis in hepatocytes and enhances vascular adhesion molecule-1 expression in liver endothelial cells promoting leucocyte migration to the inflammation site. Both of these molecules are significantly increased in CHC (25).

These results were in agreement with that of Kukla et al (26), who found that serum visfatin concentrations in CHC patients was significantly higher than that of the controls.

This study showed no correlations between serum visfatin with AST, ALT, total bilirubin and INR and a negative correlation between serum visfatin level with activity grade and stage of fibrosis in CHC patients that may propose the potential role of visfatin as a regulator of the inflammatory progression in this disease. Visfatin, can decrease the glucose level and increase insulin sensitivity, which may possible prevent the fibrotic process. Furthermore, visfatin activate matrix metalloproteinases which help removal of the extracellular matrix and control fibrosis progression (27).

The possible protective roles of visfatin against IR are increasing phosphorylation of mediators of the insulin pathway (12) and enhancing phosphorylation of insulin receptor substrate (IRS)-1 (27), which is inhibited by proinflammatory cytokines and direct action of the virus. Moreover, visfatin increases insulin receptor sensitivity (28).

In the present study, HOMA-IR values were higher in CHC patients compared to the control group. However, there was no significant correlation between serum visfatin and HOMA-IR value.

Wang et al (29) found positive correlations between visfatin, visfatin mRNA and HOMA-IR value in CHC patients with high BMI which was different from our patients with normal BMI. Serum chemerin level was significantly higher in chronic hepatitis C patients with when compared to the controls. There were significant negative correlations between serum chemerin with AST, ALT, total bilirubin and INR. Serum chemerin level was negatively associated with necro-inflammatory grade and stage of fibrosis. Kukla et al (30) proposed that chemerin may play a double role acting as a pro-inflammatory and protective factor against inflammatory hepatocyte injury.

Kukla et al (31) reported the expression of chemerin and CMKLR1 was present in the liver of all CHC patients regardless of sex or age. However this expression was not associated with necro-inflammatory activity, steatosis grade, fibrosis stage and metabolic abnormalities. They also found a negative association between serum chemerin and chemerin hepatic expression.

Yilmaz et al (32) indicated that liver injury may be associated with circulating chemerin and the liver was believed to contribute serum levels.

Chemerin may bind to its receptor on activated inflammatory cells and migrate to the inflammatory sites, exaggerating the inflammatory response and hepatocyte injury. Conversely, chemerin inhibits the release of proinflammatory TNFα and IL-6 which are upregulated in CHC. Chemerin regulates the harmful effects of these cytokines and may has a defensive role against liver injury (17).

In the current study, there was no significant correlation between serum chermerin and HOMA-IR. Similarly to Kukla et al study(29) in CHC patients.

Chemerin was describe to enhance glucose uptake and insulin receptor phosphorylation, suggesting that chemerin improves insulin sensitivity (33). Therefore, chemerin has a protective role against liver injury and fibrosis

HOMA-IR index was not linked with adipokine concentrations. The cause for this may be that adipokines are primarily from visceral adipose tissue and exhibit metabolic disturbances and the current study was carried out only in non-obese patients without metabolic disorders. This result confirms the theory that not only metabolic factors lead to the development of insulin resistance. HCV directly affects insulin signaling pathways, promoting insulin resistance at a cellular level (30,34).

Serum omentin 1 level was significantly higher in chronic hepatitis C patients when compared to the controls. There were significant positive correlations between serum omentin 1 with AST, ALT. These finding may by explained at least partially, by the implication of omentin-1 in immune and inflammatory response(31).

These results are similar to the result reported by Pan et al (35) and Nassif et al (36) who found that serum omentin 1 level positively correlated with liver enzymes (AST&ALT) so it may be implicated in hepatitis and its metabolic complications.

There was significant negative correlation between serum omentin 1 and HOMA-IR but there was no significant correlation with necro-inflammatory grade and stage of fibrosis

Yang et al (18), De Souza Bastisa et al (19), Pan et al (35), Nassif et al (36) and MacDougald & Burant (37) demonstrated that circulating omentin -1 levels have been negatively correlated with IR

Oświęcimska et al (38) revealed that serum omentin levels correlated negatively with BMI, serum insulin, and HOMA-IR index and they suggested that omentin is the nutritional marker exhibiting body weight and insulin resistance.

Herder et al (21) proposed that omentin operates by control of adiponectin, which consecutively influence lipid metabolism and also indirectly improves insulin sensitivity.

Kukla et al (39) found that serum omentin1 levels were significantly higher in CHC patients compared to controls regardless of sex, body mass index (BMI), insulin sensitivity and lipid concentrations. There was no correlation between serum omentin and omentin hepatic expression. Neither parameter was related with any histological features. Serum omentin in non-obese CHC patients seems not to be linked to metabolic disorders or liver pathology. Omentin hepatic expression shows no connection with either serum omentin 1levels or histo-pathological features. This proposes different mechanisms regulating circulating omentin 1concentration and omentin hepatic expression in CHC.

CONCLUSIONS

Serum visfatin, chemerin, omentin-1 levels were significantly elevated in chronic hepatitis C patients. Serum visfatin and chemerin may play a pivotal role in CHC pathogenesis and their concentrations may serve as an additional tool in determining more advanced grades of necro-inflammatory activity and stage of fibrosis. While serum omentin-1 can predict the insulin resistance in CHC patients.

RECOMMENDATIONS

Further research is also required on a wide scale of patients to evaluate the real value of visfatin and chemerin as pharmacological target to reduce inflammation and stage of fibrosis. While serum omentin1 should be evaluated to decrease insulin resistance in CHC patients.

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